IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Barras et al.		
Serial No.:	10/693,328	ART UNIT:	1614
Filed:	October 24, 2003	EXAMINER:	Royds, Leslie
Entitled:	COLON CLEANSING COMPOSITIONS		

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DECLARATION OF THOMAS J. BORODY, M.D., Ph.D.
UNDER 37 C.F.R. §1.132

I, Thomas J. Borody, hereby declare and state that:

1. I am the inventor of the subject matter claimed in international publication WO 89/05659, which is cited in the current proceedings. The international application resulted in the grant of US Patent No. 5,274,001. In a patent license agreement dated August 19, 1998 and amended on May 8, 2002, I granted to Norgine BV. a company in the same group of companies as the current assignee of the present application (US Ser. No. 10/693,328), an exclusive license to develop, manufacture, and sell products within the scope of the '001 patent. I have subsequently agreed to assign the '001 patent to Norgine. I had no involvement in the invention set forth in the present application Ser. No. 10/693,328, and, other than the relevance of my patent publication as prior art, I had no involvement in the conception, development or testing of the products contemplated by the present application. Nor do I have any financial interest in the present application; no payment has been made to me and there is no payment due to me which is contingent upon the granting of the present application in the United States or its equivalent elsewhere.

2. I presently hold the position of Adjunct Professor at the University of Technology, Sydney, Australia. I have been active in the development of new products in the field of gastroenterology for many years. A copy of my *curriculum vitae* is attached as exhibit A.

3. I am familiar with the subject matter claimed in the above-identified patent application, U.S. Serial No. 10/693,328.

4. I have been informed and understand that the last Office Action issued in this application was dated February 17, 2006 and that the Examiner of this application is of the view and stated in the Office Action that the presently claimed subject matter is considered unpatentable as obvious over my international publication WO 89/05659 in further view of Fordtran, international publication WO 87/00754 (hereinafter "Fordtran"), US Patent No. 5,458,890 issued to Williford et al., Stedman's Medical Dictionary (22nd Edition, 1972, page 737), and the Merck Index (Monograph 8723, 1996). I make this declaration to provide facts that I believe are probative of the issues raised by the rejection.

5. The subject matter of application Ser. No. 10/693,328 relates to advanced bowel lavage solutions. Early bowel lavage solutions were "balanced electrolyte solutions" - essentially large quantities of water with dissolved electrolytes. It was found, however, that they resulted in significant absorption of water and sodium into the body (as set out, for example, in Davis et al., 1980, *Gastroenterology*, 78(5), 991-995 (copy attached as Exhibit B)). Davis et al. used as a control a "balanced electrolyte solution" (termed "BES" in Table 2 in the paper) consisting of 110 mM NaCl, 30 mM $NaHCO_3$, 10 mM KCl and 5g/litre PEG. Infusion of that solution was found to be associated with net water absorption of 819 ml/hr and net sodium absorption of 127 mEq/hr.

6. Davis et al. then found that the absorption of water and sodium could be reduced by including mannitol or by replacing much of the sodium chloride in the balanced electrolyte solution with sodium sulfate, a sodium composition that crosses the intestinal membrane only very poorly due to the membrane impermeability of the sulfate anion. They also found (in solution E) that the mannitol could be replaced with an osmotically equivalent amount of PEG (59 g/litre).

7. Those solutions developed by Davis et al. had fewer side effects than the balanced electrolyte solutions and they established two general principles that were to guide orthostatic lavage solutions in the coming decades:

   1) The solution should not contain a large concentration of sodium in an absorbable form (*e.g.* as sodium chloride) to keep sodium absorption to a minimum; and
   2) The solution should have the *same total osmolarity as the blood* to keep water absorption and water secretion to a minimum.

8. The osmolality of the plasma varies slightly from individual to individual and over time for an individual, but typically it is approximately 290 mOsm/kg, (as set out ,for example, in *Gastrointestinal Disease Pathology/Diagnosis/Management*, Vol 2, Ed:J.S.Fordtran, Chapter 49, page 1051, column 2, line 46, copy attached as exhibit C). Variations are rarely more than +/- 8mOsm/kg.

9. As disclosed in my international publication WO 89/05659, I discovered, *inter alia*, that the effectiveness of bowel lavage solutions was improved by including ascorbic acid or a salt thereof. In formulating such solutions, I continued to adhere to the guidelines established by Davis et al. in regards to osmolarity, *i.e.*, the solution should have the same or similar total osmolarity as the blood to keep water absorption and water secretion to a minimum.

10. Bowel lavage solutions according to Davis et al. have appeared as commercial products, such as those sold under the name GOLYTELY.

11. In an effort to reduce the saltiness of the taste of the Davis / GOLYTELY solution, Fordtran (*see* 1990, *Gastroenterology*, 98, 11-16 and WO 87/00754) investigated replacement of the sodium sulfate in that solution with additional PEG. That gave rise to a solution given the name GOLYTELY-RSS (RSS signifying reduced sodium solution) that has a relatively low concentration of sodium (65 mM) and a high concentration of PEG (105 g/litre). The solution was found to be more palatable than GOLYTELY. A high PEG solution using the teaching of Fordtran is also marketed, under the name NuLYTELY. The calculated osmolarity of a NuLYTELY solution (47 mM NaCl, 5 mM KCl, 17 mM $NaHCO_3$, 105 g/L PEG) is relatively low, but as set out in Table 1 of the Fordtran paper, because of the particular non-linear osmolarity properties of PEG, the

measured osmolality is actually 288 mOsmol/kg. That solution thus also adheres to the guidelines established by Davis et al.

12. In the Fordtran patent publication (WO 87/00754) a broad range of PEG concentrations is claimed. It is clear, however, that isosmolarity is an important characteristic of the solutions. Example 3 is a solution which contains contains 120 g/L of PEG made up with electrolytes to create a solution which has a measured osmolarity of 293 mOsmol/kg (page 14, line 6). In moving to example 4, Fordtran reduced the concentration of PEG to 105 g/L (page 15, line 10). At the same time Fordtran adjusted the concentrations of the electrolytes in example 4 in order to maintain the iso-osmolarity of the resulting solution (example 4 is identical to the GoLytely-RSS solution in the Fordtran paper in *Gastroenterology*, which states that the solution has a measured osmolality of 288 mOsmol/kg). Thus, Fordtran continued to adhere to the Davis et al. iso-osmolarity guidelines in the preparations he actually proposed to administer to patients.

13. Thus, at the time of the invention described in Ser. No. 10/693,328, all "balanced electrolyte" type bowel lavage solutions on the market did not contain a large concentration of sodium in an absorbable form (*e.g.*, as sodium chloride) and they had the same total osmolarity as the blood to keep water absorption and water secretion to a minimum, *i.e.*, they were all iso-osmotic solutions.

14. As an alternative to the balanced electrolyte bowel lavage products, other solutions were introduced which operated on a different physiological mechanism. The alternative bowel lavage formulations are very *hyper*osmotic solutions which utilize highly concentrated solutions of salts, especially sodium phosphate, that are taken in a relatively small volume (20 to 45 mL). These extremely hyperosmotic solutions (e.g., having osmolarities of well over 2000 mOsm/kg) operate by causing a large amount of water being drawn from the blood volume of the patient into the bowel, and it is this water that flushes the colon. Such solutions have the advantage of requiring only a small quantity of liquid to be ingested, therefore patient compliance is generally high. The best example of such super-hyperosmotic solutions is the commercial product PHOSPHOSODA, which contains, in a 90 ml dose (2 x 45 ml), i.e., the dose generally used for colon cleansing, 43.2 g monobasic sodium phosphate monohydrate with 16.2 g dibasic sodium phosphate heptahydrate. The osmolarity of such compositions is over 2000 mOsmol/kg

15. I am aware of improvements on the PHOSPHOSODA product having been described, for example, in Cleveland, US Patent No. 6,946,149. The solutions of Cleveland resulted in a similar loss of water from the body as the sodium phosphate solutions typified by PHOSPHOSODA. Cleveland proposed adding a small quantity of PEG to reduce the amount of salts necessary for effective colon cleansing. However, the solutions of Cleveland were similarly super-hyperosmotic, having calculated osmolarity of over 2300 mOsm/kg.

16. Because the super-*hyper*osmotic solutions have such a significant effect on water movement, they also have a significant effect on blood electrolyte levels. Typically, a dose of a super-hyperosmotic sodium phosphate solution results in the loss of 2.5 litres of water from the body and a change in serum electrolyte levels. For example, a typical dose of PHOSPHOSODA results in an increase in serum phosphate concentration from 2.8 to 6.5 mg/dL (Kolts et al., 1993, *Am . J. Gastroenterology*, 88, 1218-1223). For these reasons, super-hyperosmotic sodium phosphate solutions are contraindicated for elderly patients and some other patient groups because of the risk of kidney damage, hyperphosphatemia, hypocalcemia or hypokalemia.

17. In summary, the solutions known prior to the invention of application Ser. No. 10/693,328 can be grouped into two categories:
    1) Large volume, isosmotic, PEG-containing balanced electrolyte bowel lavage solutions; and
    2) Low volume, super-hyperosmotic concentrated salt solutions, typified by sodium phosphate solutions.

18. I continued to believe that iso-osmolarity was an important feature of lavage solutions until I became aware of the invention described in application Ser. No. 10/693,328. I have carried out work myself in attempts to improve the prior art solutions, and whenever I have instructed pharmacists to make up formulations of lavage solutions I have always issued very particular instructions to make sure that the osmolarity of the solutions remains in the range 288 to 298 mOsm/kg, *i.e.* iso-osmolar. Any changes I considered making to the make-up of the formulation were always carried out in such a way that the composition retained its iso-osmolarity. For example, if I introduced an ingredient that

increased the osmolarity, I would then reduce the concentration of another ingredient to maintain the total osmotic load.

19. When I made the invention described and claimed in my publication WO 89/05659, my experiments were based on formulations that included ascorbic acid. I included mention of salts in the patent application because I was aware that ascorbic acid could be generated *in situ* in the stomach after ingestion of a salt of ascorbic acid. I did not contemplate a formulation including a combination of both ascorbic acid and a salt thereof. I was not aware of, nor did I foresee, any advantages of including both ascorbic acid and a salt thereof based on my knowledge of the art or any data from my own work. That remained my view until I became aware of the invention described in Ser. No. 10/693,328.

20. In accordance with my experience in this field and my knowledge of the state of the art at the time the invention of Ser. No. 10/693,328 was made, it is clear that the inventors broke with long-established teachings in the field to prepare solutions that were not iso-osmotic, instead having an osmolarity in the range of 300 – 700 mOsmol/kg, yet the solutions were effective for bowel cleansing. Moreover, such solutions necessarily caused some secretion of water but evidently did not lead to the electrolyte imbalances or risks of products such as PHOSPHOSODA, yet they are effective for bowel cleansing. In addition, the inventors of the compositions of Ser. No. 10/693,328 have discovered an advantage to including both ascorbic acid and a salt thereof in the same formulation, relating to maintenance of plasma bicarbonate levels, as explained at the end of Example 2 in their application. I regard these as significant advances in the field.

21. I further declare that all statements made herein of my own knowledge are true and that statements made upon information and belief are believed to be true and further that false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

1/05/06
date

DECLARANT

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Professor Thomas J. Borody

Personal Information	Place of Birth:	Krakow, Poland
	Citizenship:	Australian
Education	1971	BSc(Med) Hons, University of New South Wales, Sydney
	1974	MBBS (Hons), University of New South Wales, Sydney
	1982	FRACP, Royal Australasian College of Physicians
	1984	MD, University of New South Wales, Sydney
	1993	FACG, American College of Gastroenterology
	2002	FACP, American College of Physicians
	2005	PhD, The University of Newcastle
Professional Training	1974	INTERNSHIP St Vincent's Hospital, Sydney
	1975 – 1977	RESIDENCY St Vincent's Hospital, Sydney,
	1981 – 1983	FELLOWSHIP St Vincent's Hospital, Sydney
Research Training	1971	RESEARCH FELLOW Pathology Dept, University of New South Wales, Sydney
	1979 – 1980	National Health & Medical Research Council (NH&MRC) POSTGRADUATE SCHOLAR Garvan Institute of Medical Research, Sydney
	1983 – 1984	FELLOW IN GASTROENTEROLOGY – NH&MRC SCHOLAR Mayo Clinic, Rochester, MN, USA
Scholarships, Awards and Grants	1971	National Heart Foundation Scholarship
	1979	NH&MRC Postgraduate Scholarship
	1981	Young Investigator Award, Gastroenterological Society of Australia (GESA)
	1982	Winthrop Travelling Fellowship (Royal Australian College of Physicians)

	1983	Neil Hamilton Fairley Fellowship (NH&MRC)
	1986	NH&MRC Project Grant
	2002	Marshall & Warren Prize for Best Poster Australian Gastroenterology Week
Professional Appointment	1978	MEDICAL OFFICER (Tropical Gastroenterology Training) Atoifi Adventist Hospital, Malaita, Solomon Islands
	1981	MEDICAL REGISTRAR St Vincent's Hospital, Sydney
	1982	SENIOR MEDICAL REGISTRAR St Vincent's Hospital, Sydney
	1985 – Current	DIRECTOR and GASTROENTEROLOGIST Centre for Digestive Diseases, Five Dock, Sydney (est. 1985)
	1996 – 2002	CONSULTING GASTROENTEROGIST St Vincent's Hospital, Sydney
	1995 – Current	CONSULTING GASTROENTEROGIST Sydney Adventist Hospital, Wahroonga
	2004 - Current	ADJUNCT PROFESSORSHIP University of Technology, Sydney
Professional memberships	Since 1974	Australian Medical Association
	Since 1981	GESA
	Since 1991	European Gastroenterology Society
	Since 1991	Functional Brain-Gut Research Group
	Since 1993	American College of Gastroenterology
Medical Licensure	1974 – Current	New South Wales Registration, Australia
	1984 – Current	FLEX/Minnesota Licence, USA

Reviewer For

American Journal of Gastroenterology

Digestive Diseases and Sciences

Endoscopy

Journal of Gastroenterology and Hepatology

Medical Journal of Australia

Digestive and Liver Diseases

Research Interests and Activities

Principal or co-investigator in over 30 Clinical research trials, all of which have been conducted according to ICH/GCP guidelines.

Current research interests include:

1. *Helicobacter pylori* associated disorders
2. Novel therapies for Inflammatory Bowel Disease and Irritable Bowel Syndrome
3. Bacteriotherapy
4. Development of Colon Lavage Products

Patents

Over 24 patents in areas such as; treatment of *Helicobacter pylori*, Crohn's disease, bowel lavage, IBS and bacteriotherapy.

Publications

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12. Bacteriotherpay using fecal flora: toying with human motions. **TJ Borody**, EF Warren, SM Leis, R Surace, O Ashman, S Siarakas. J CLin Gastroenterol 2004; 38(6):475-83

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Development of a lavage solution associated with minimal water and electrolyte absorption or secretion.

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Development of a Lavage Solution Associated with Minimal Water and Electrolyte Absorption or Secretion

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Ingestion of large volumes of a balanced electrolyte solution has previously been shown to be an effective method of cleaning the colon for diagnostic studies. However, in this paper we have shown that total gut perfusion with such a solution results in absorption of 2400 ml water and 375 meq of sodium over 3 hr, which is the approximate time required to clean the colon by this technique. This might be hazardous to patients who are unable to readily excrete a salt and water load. We, therefore, designed a solution containing mainly sodium sulfate that was associated with only trivial amounts of water and sodium absorption or secretion during total gut perfusion. This new solution might be useful in colon cleansing before colonoscopy, barium enema, and surgery. In addition, such a solution may have some therapeutic indications, including bowel cleaning in patients with hepatic encephalopathy or as a rapid washout technique for ingested toxins.

Rapid ingestion of large volumes of saline or a balanced electrolyte solution causes diarrhea and has been used as a method for cleaning the colon before barium enema,[1-3] colonoscopy,[4] or colon surgery.[5] Theoretically, such total gut perfusion might also be useful for bowel cleaning in patients with hepatic encephalopathy and for rapid washout of ingested toxins. However, a significant fraction of these solutions may be absorbed resulting in rapid weight gain of 1.1–2.3 kg.[1,2,6] This method of cleaning the colon may therefore be dangerous in patients who are unable to normally excrete salt and water loads. Alternate methods of cleaning the colon include the use of cathartics and enemas, but these are associated with potentially hazardous loss of salt and water from the body.[1,7]

It was the purpose of these experiments to design a solution for intestinal lavage that would not be absorbed from the intestine or induce a loss of salt and water from the body.

Materials and Methods

After an overnight fast, normal subjects swallowed a polyvinyl tube. The infusion site was located in the midstomach, and the solution to be evaluated was warmed to room temperature and infused at pump speed of 20 or 30 ml/min. Actual measured infusion rates differed slightly from the pump speed settings. These solutions contained various combinations of NaCl, Na_2SO_4, $NaHCO_3$, and KCl and 5 g/liter PEG as a nonabsorbable marker. In addition, they contained mannitol in quantities sufficient to result in an osmolality of approximately 280 mOsmol/kg. In one solution, a higher concentration of PEG 4000 (carbowax) was used as a solute to replace the mannitol.

Twenty minutes after starting, infusion of the test solution was momentarily interrupted and 200 mg of sulfabromophthalein (BSP) was injected into the stomach through the polyvinyl tube. When watery diarrhea ensued, the stool specimens were checked for BSP by alkalinization with sodium hydroxide. When all BSP had been eliminated, we assumed that a steady state of perfusion had been achieved. It was observed that the rectal effluent became clear of feces at the same time when BSP was no longer present. The perfusion was continued for 3 hr beyond this time. This 3-hr period consisted of six 30-min collection periods during which PEG concentrations remained essentially the same, giving evidence of a "steady

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state." The collected samples of rectal effluent were analyzed for PEG, osmolality, and electrolytes by standard methods," and net water and electrolyte movement was calculated with the use of standard nonabsorbable marker equations." Significance of difference was determined by group t-analysis.

All studies were approved by the Human Research Review Committee at our institution in August 1978.

Results

Preliminary Studies

The first four test solutions (A–D) were infused at a rate of 20 ml/min, each in a different subject. As shown in Table 1, total gut perfusion with solution A resulted in prominent secretion of water and bicarbonate, so to solution B we added $NaHCO_3$ and decreased the mannitol and Na_2SO_4 concentration. With solution B there was absorption of water and sodium, so mannitol and Na_2SO_4 were increased and $NaHCO_3$ was decreased in solution C. Perfusion of solution C was associated with moderate sodium and bicarbonate absorption, so a further fine adjustment was made by decreasing the Na_2SO_4 and $NaHCO_3$ and increasing mannitol by small amounts to make solution D. Solution D was associated with mild secretion of water (60 ml/hr) and near zero net movement of electrolytes.

Comparison of Solution D and a Balanced Electrolyte Solution

Solution D appeared to approximate the requirements set out as the objective of the experiment; that is, when perfused at a constant rate, this solution was associated with negligible net water and electrolyte movement, at least in one preliminary experiment. We then studied solution D in 5 normal subjects; infusion rates of 20 and 30 ml/min were used to determine the influence of infusion rate on water and electrolyte movement with the solution. For comparison, a balanced electrolyte solution consisting of 110 mM NaCl, 30 mM $NaHCO_3$, 10 mM KCl, and 5 g/liter PEG was infused at a rate of 30 ml/min in 5 normal subjects. This solution is similar in composition to those used by others to clean the colon.[1]

The average result of perfusing solution D at a rate of 20 or 30 ml/min in 5 normal subjects was similar (Table 2); that is, the net movement of water and electrolytes was trivial at both rates. By comparison, infusion of the balanced electrolyte solution (BES) was associated with mean net water and sodium absorption rates of 819 ml/hr and 127 meq/hr, respectively (Table 2). Results in the individual subjects for water and sodium movement are shown in Figure 1.

Results in Special Patients

Solution D was infused in 1 patient with cirrhosis and portal hypertension with ascites and in 1 patient with chronic renal failure on hemodialysis. As shown in Figure 1 and Table 2, results in these patients were similar to results in the normal subjects.

Substitution of PEG for Mannitol

There is some concern that mannitol may be metabolized by bacteria in the intestine and could potentially produce explosive gases (see Discussion). We therefore replaced mannitol (in solution D) with an osmotically equivalent amount of PEG (59 g/

Table 1. *Water and Electrolyte Movement with Test Solutions During the Preliminary Studies[a] (Infusion Rate 20 ml/min)*

Solution[b]	Water (ml/hr)	Na (meq/hr)	K (meq/hr)	Cl (meq/hr)	HCO_3 (meq/hr)
A	+258	+19	+4	−4	+28
B	−138	−34	−3	−5	−20
C	−48	−21	−2	−1	−14
D	+60	+7	−3	+4	+3

[a] (+) indicates net secretion; (−) indicates net absorption.

[b] Composition and osmolality of test solutions:

	NaCl (mM)	Na_2SO_4 (mM)	KCl (mM)	$NaHCO_3$ (mM)	Mannitol (mM)	PEG (g/liter)	Osmol (mOsmol/kg)
A	45	47.5	5	—	90	5	279
B	25	37.5	10	35	67.5	5	279
C	25	42.5	10	25	75	5	282
D	25	40.0	10	20	80	5	273

Table 2. Net Movement of Water and Electrolytes (Mean ± Standard Error)

Subjects	No. of subjects	Solution	Measured infusion rate (ml/min)	Water (ml/hr)	Na	K	Cl	HCO_3
					(meq/hr)			
Normal	5	BES	30 ± 1	−819 ± 29	−127 ± 4	−10 ± 1	−110 ± 6	−26 ± 2
Normal	5	D	28 ± 1	+56 ± 35[d]	0 ± 7[d]	0 ± 1[d]	+11 ± 5[d]	−5 ± 2[e]
Normal	5	D	20 ± 1	−20 ± 40[d]	−7 ± 6[d]	−1 ± 2[d]	−2 ± 5[d]	−4 ± 2[e]
Liver disease[b]	1	D	29	+78	−5	−1	+8	−2
Renal disease[c]	1	D	20	−137	−26	−1	−8	−7
Normal	5	E	28 ± 1	−130 ± 40[d,f]	−8 ± 8[d]	−3 ± 1[d]	+8 ± 4[d]	−10 ± 1[e,g]

[a] (+) = net secretion; (−) = net absorption. [b] Represents one study in this patient. [c] Values represent mean of three studies in 1 patient. [d] $P < 0.001$ when solution compared with solution BES. [e] $P < 0.05$ when solution compared with solution BES. [f] $P < 0.01$ when solution compared with solution D infused at 28 ml/min. [g] $P < 0.025$ when solution compared with solution D infused at 28 ml/min.

liter). This was called solution E, and it was perfused in 5 normal subjects. As shown in Figure 1 and Table 2, perfusion of solution E was also associated with minimal net water and electrolyte movement.

Other Results

In normal subjects there was no significant change in hemoglobin concentration, hematocrit, or serum electrolytes during administration of any of these solutions. Similarly, no changes were seen in the patient with ascites or the patient with chronic renal failure.

The rectal effluent rate was significantly less with the BES at 30 ml/min than with solution D or E when the pump speed was set at 30 ml/min ($P < 0.001$).

There was a mean weight gain of 0.54 kg for each hour of perfusion with BES (Table 3). With D, there was essentially no change in weight regardless of infusion rate in either the normal subjects or the patients with ascites and chronic renal failure. Likewise with solution E, there was essentially no change in weight in normal subjects.

The time required to obtain a clear rectal effluent (which coincided with the disappearance of BSP) is also shown in Table 3. At a pump speed of 30 ml/min, the rectal effluent became clear in a mean time that was shorter with solution D than with BES ($P = 0.05$).

Discussion

As shown in this study, total gut perfusion with a balanced electrolyte solution results in substantial absorption of sodium, chloride, and water. For example, if a patient were to ingest a balanced electrolyte solution for 3 hr at a rate of 1.8 liters/hr (30 ml/min), which is the average time required to clear the colon, he or she would absorb about 2.4 liters of water and about 375 meq of sodium. This might be dangerous if the patient was not able to readily excrete the salt and water load.

The purpose of the present study was to design a solution for total gut perfusion that would not be associated with net water or electrolyte absorption or secretion. We were able to design such a solution, with sodium sulfate as the predominant salt. The electrolyte concentrations in our solutions were as follows (in meq/liter): Na = 125; SO_4 = 80; Cl = 35; HCO_3 = 20; and K = 10. The solution also contained 80 mM of a poorly absorbed nonelectrolyte (mannitol or PEG).

How can the near zero water and sodium movement seen with this particular solution be explained? It is known that sodium is actively absorbed (against an electrochemical gradient) by the intestinal mucosa when its accompanying anion is chloride.[9] However, active sodium absorption is markedly reduced when sulfate is substituted for chloride[10] as in our solution, and sulfate itself is a poorly absorbed anion.[11] In addition, during perfusion of our solution there was a slight sodium con-

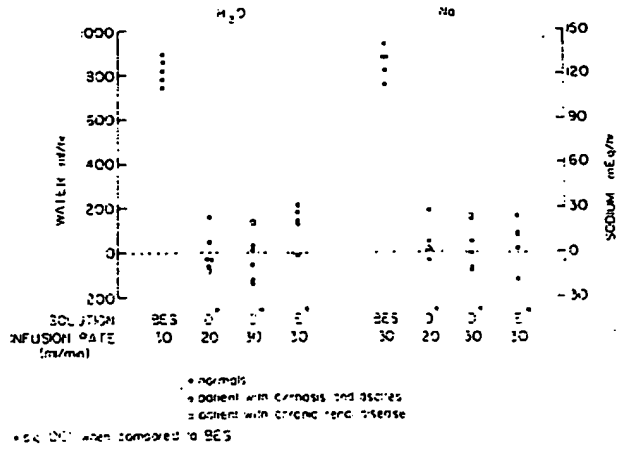

Figure 1. Net water and sodium movement during total gut perfusion with balanced electrolyte solution (BES), solution D, and solution E (see text for composition).

(± = Standard Error)

Subjects	No. of subjects	Solution	Measured infused rate (ml/min)	Rectal effluent rate (ml/min)	Weight change (kg/hr of perfusion)	Time required to reach steady state (hr)
Normal	5	BES	30 ± 1	15.9 ± 0.9	+0.54 ± 0.05	3.1 ± 0.3
Normal	5	D	28 ± 1	29.1 ± 0.7[c]	−0.04 ± 0.05[c]	2.2 ± 0.3[d]
Normal	5	D	20 ± 1	18.0 ± 0.8	−0.02 ± 0.05[c]	3.2 ± 0.4
Liver disease[a]	1	D	29	30.2	−0.09	2.5
Renal disease[b]	1	D	20	19.4	+0.07	3.2
Normal	5	E	28 ± 1	27.4 ± 0.7[c]	+0.03 ± 0.03[c]	2.8 ± 0.1

[a] Represents one study in this patient. [b] Mean value of three studies in 1 patient. [c] $P < 0.001$ when compared with solution BES. [d] $P = 0.05$ when compared with solution BES.

centration gradient (plasma 140, luminal solution 125 meq/liter), and this must have resulted in a small amount of passive sodium secretion. Presumably, this small passive sodium secretion was balanced by a small amount of active sodium absorption, since net sodium movement was approximately zero when this test solution was perfused through the gut.

Potassium movement in the GI tract is mainly passive, in response to chemical and electrical gradients.[12] Since the sodium concentration in our solution was only slightly different from that of plasma, no sodium diffusion potential would be expected during its perfusion through the gut.[9] Also, sulfate substitution for chloride in intestinal contents does not result in a change in PD.[10] Therefore, perfusion of our solution would not be expected to alter substantially the electrical gradient across the mucosa, and thus should not have a marked influence on potassium movement. Therefore, only 10 meq/liter of potassium had to be added to our solution to prevent net potassium loss during its perfusion. Presumably, the proximal small bowel absorbed enough of the potassium in the solution (in response to the concentration gradient from lumen-to-plasma) to compensate for potassium secretion in the colon (in response to the lumen negative PD which normally exists across colonic mucosa).

Bicarbonate is normally secreted into the lumen of the ileum and colon, whereas bicarbonate is actively absorbed from the proximal small bowel. By incorporating 20 meq/liter of bicarbonate into our solution, proximal bicarbonate absorption presumably cancelled distal bicarbonate secretion. Chloride movement is passive in the proximal small bowel, but chloride is actively absorbed (against steep concentration gradients) in the ileum and colon.[10] We found that 35 meq/liter of chloride had to be added to our test solution in order to obtain an overall net chloride movement of near zero during total gut perfusion. Presumably, chloride was secreted passively in the proximal small bowel in response to the plasma-to-lumen concentration gradient, and an equivalent amount was actively reabsorbed in the ileum and colon.

Isonatremic solutions of sodium sulfate are hyposmotic to plasma because plasma anions are monovalent, whereas sulfate is divalent. If such a hypotonic solution was perfused through the gut, there would be a tendency for water to be absorbed. Therefore, we added a nonabsorbable solute, mannitol, to our solution in order to render it isosmotic. Mannitol served its purpose well, since whole gut perfusion with this solution resulted in essentially no net absorption or secretion of water.

Mannitol is fermentable and its metabolism by colonic bacteria yields hydrogen, an explosive gas.[13] Consequently, preparation of the colon with mannitol-containing solutions might be hazardous in patients who are to undergo colonoscopy with electrocautery.[13,14] We therefore needed to find a substitute for mannitol that cannot be metabolized by colon bacteria. We selected PEG for this purpose because it is nonabsorbable and Dr. Michael Levitt showed that fecal suspensions do not generate hydrogen when incubated with PEG (personal communication). Total gut perfusion with this modified solution was also not associated with significant salt and water absorption. This solution might, therefore, be useful in cleaning the colon of patients who are about to undergo colonoscopy, and its perfusion probably will not result in accumulation of potentially explosive gases.

Most of our studies were done in normal subjects. However, similar results were obtained in 1 patient with presumed secondary aldosteronism (cirrhosis with ascites) and in 1 patient with endstage renal disease. Both patients tolerated the solution well, without evidence of clinically significant salt and water absorption or secretion. Although there is no reason to believe that such patients will react differently than normal people to total gut perfusion with our solutions, this experience with compromised patients is obviously limited, and further clinical trials

are needed before it can be assumed that such solutions will not adversely affect these individuals.

In these experiments, we infused the test solution into the stomach at a constant rate in order to accurately measure absorption and secretion rates under steady-state conditions. Since the results were essentially the same when the infusion rate was 20 or 30 ml/min, oral ingestion of the solution at 20–30 ml/min (1.2–1.8 liter/hr) should result in essentially no water or electrolyte absorption or secretion.

Both solutions taste better when they have been refrigerated. The cost of the ingredients (reagent grade) is $2.50–$5.00 per 5 liters, depending on whether mannitol or PEG is used as the poorly absorbed nonelectrolyte.

All solutions worth their salt need a name. We call ours "Golytely."

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Exh. C

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Chapter 49

DIARRHEA

KENNETH D. FINE, GUENTER J. KREJS, and JOHN S. FORDTRAN

DEFINITION

The word *diarrhea* originates from the Greek terms *dia* (through) and *rhein* (to flow). Dorland's Medical Dictionary defines diarrhea as an abnormal frequency *and* liquidity of fecal discharges.[1] In our opinion, it is best to define diarrhea simply as an abnormal looseness of the stools (increased liquidity or decreased consistency). Diarrhea so defined is usually accompanied by an abnormal increase in daily stool weight (>235 gm/day in men, >175 gm/day in women) and by an abnormal increase in bowel movement frequency (≥2 times per day).[2] Patients with diarrhea often have associated symptoms of abdominal pain, urge to defecate, perianal discomfort, and fecal incontinence. With moderate to severe diarrhea, many patients lose weight, probably due to reduced food intake. With severe or protracted diarrhea, volume depletion and electrolyte disturbances often develop.

Confusion regarding definition may develop in rare cases when patients have daily stool weights that exceed the upper limit of normal yet have normal stool consistency. Neither Dorland's definition nor ours would label this as diarrhea. Excessive fiber ingestion is the most likely explanation, but steatorrhea could theoretically also produce this paradox. Some people with formed stools have three or more bowel movements per day. Although this may represent an abnormality of bowel function, it does not meet either definition of diarrhea. Finally, some patients have abnormally loose stools but do not have more than two bowel movements per day; by our definition, but not by Dorland's, this constitutes diarrhea.

FOUR MAJOR MECHANISMS OF DIARRHEA

There are four major mechanisms of diarrhea[3]: (1) the presence in the gut lumen of unusual amounts of poorly absorbable, osmotically active solutes (osmotic diarrhea); (2) intestinal ion secretion or inhibition of normal active ion absorption (secretory diarrhea); (3) deranged intestinal motility; and (4) exudation of mucus, blood, and protein from sites of inflammation.

Osmotic Diarrhea

Osmotic diarrhea is caused by ingestion of a poorly absorbable solute, usually a carbohydrate or a divalent ion as shown in Table 49–1. A hypothetical example is shown in Figure 49–1. A patient ingests 250 ml of fluid

TABLE 49–1. SOME CAUSES OF OSMOTIC DIARRHEA

A. Carbohydrate malabsorption from:
   1. Generalized malabsorption syndrome
   2. Disaccharidase deficiencies
   3. Congenital glucose-galactose malabsorption
   4. Congenital fructose malabsorption

B. Excessive ingestion of poorly absorbed carbohydrate
   1. Lactulose therapy
   2. Sorbitol* in elixirs; "sugar-free" gum or mints; or from pears, prunes, peaches, and orange juice
   3. Fructose* from soft drinks, apples, pears, honey, cherries, dried dates, dried figs, grapes, pears, prunes
   4. Mannitol in sugar-free products, mints
   5. Bran/fiber

C. Mg-induced diarrhea from:
   1. Food supplements
   2. Antacids
   3. Laxatives

D. Laxatives containing poorly absorbable anions:
   1. Sodium sulfate (Glauber's salt)
   2. Sodium phosphate
   3. Sodium citrate

*Data on the sorbitol and fructose content of various foods, gums, and drinks can be found in Gastroenterology *84*:30, 1983; J. Pediatr. *103*:575, 1983; Arch. Dis. Child *59*:735, 1984.

diary of bowel activity so that stool weight per movement can be estimated, and a diary of food and liquid intake so that calorie, fat, carbohydrate, and/or fiber intake can be estimated from dietary tables. There should be no diagnostic test (e.g., lactose tolerance test, D-xylose test, or barium studies) that would disturb the normal eating pattern, add foreign material to the gut, or risk an episode of incontinence. All but essential medications are avoided.

It should be remembered that the stools of a patient may vary considerably from day to day and week to week. When evaluating the results of quantitative stool analysis, one needs to know whether the submitted stool was collected during a time that the patient was having what he or she considers to be diarrhea. It is advantageous for the physician to actually see the collected specimen, since the definition of diarrhea depends on the subjective opinion that stool consistency is abnormally loose or liquid.

Knowledge of stool weight may help to clarify the nature of the patient's problem and to localize the region of the intestine most likely to be responsible for the diarrhea. In some instances, knowledge of stool weight is of direct help in diagnosis and management. For example, stool weights greater than 500 gm/day are rarely if ever seen in patients with irritable bowel syndrome,[27, 28] and stool weights of less than 1000 gm/day are evidence against pancreatic cholera syndrome. Also, very high stool weights alert the physician to the possible need for vigorous fluid replacement. Low stool weight in a patient with "severe diarrhea" suggests that incontinence or pain may be the dominant aspect of the patient's problem.

In special instances, it is useful to determine whether diarrhea persists during a 48-hour fast, while the patient is given glucose and salt solutions intravenously (see above under Secretory and Osmotic diarrheas).

Quantitative Fecal Fat Excretion. The amount of fat in stool is usually quantitated by the titration method of van de Kamer.[29] In most clinical laboratories, the upper limit of normal for fecal fat measured in normal subjects ingesting normal amounts of dietary fat is about 7 gm/day.[28, 30–33] By definition, values greater than this are abnormal and signify the presence of steatorrhea. However, in a study of normal subjects, induced diarrhea often caused fecal fat excretion to rise above the upper limit of normal[33]; this occurred in 21 per cent (6 of 29) of subjects with mild to moderate diarrhea (fecal weight ≤800 gm/day) and in 58 per cent (11 of 19) of subjects with severe diarrhea (fecal weight >800 gm/day). Thus, even when mechanisms of digesting and absorbing dietary fat are intact, diarrhea *per se* frequently causes what can be termed secondary steatorrhea, with values as high as 13.6 gm/day. Therefore, in patients with diarrhea, an abnormal fecal fat value between 7 and 14 gm/day will have a low specificity for accurately diagnosing primary defects in fat digestion or absorption. On the other hand, abnormal results of 14 gm/day or higher will be more specific for diseases that impair fat digestion and/or absorption (i.e., diseases of the exocrine pancreas, the small intestinal mucosa, and the enterohepatic circulation of bile salts).

Fecal Electrolytes, Osmotic Gap, and Osmolality. These measurements are made in supernatant (stool water) obtained after a stool sample is centrifuged. Since the results are expressed in concentration terms, the analysis can be done and the results interpreted from spot samples or from specimens collected quantitatively over 24 to 72 hours.

In secretory diarrhea, the fecal fluid should be rich in monovalent electrolytes since secretion of electrolytes or failure to absorb electrolytes is the primary cause of the diarrhea. By contrast, osmotic diarrhea is caused by the osmotic effect of poorly absorbed solutes that are ingested in the diet or as medication. In osmotic diarrhea, the fecal fluid is rich in the ingested nonabsorbable solute and should have a low concentration of electrolytes. In principle, therefore, secretory and osmotic diarrhea can be differentiated by measurement of fecal electrolytes.

The monovalent electrolyte composition of fecal fluid can be estimated by the sum of the sodium and potassium concentrations, multiplied by a factor of 2 to account for associated anions. When this value is subtracted from fecal osmolality, the "osmotic gap" is derived; the osmotic gap should be large in osmotic diarrhea and small in secretory diarrhea. Originally, the calculation of fecal osmotic gap was performed by using the measured osmolality of fecal fluid.[3] This entails several problems. First, fecal fluid osmolality rises progressively from the time feces are emptied from the rectum, owing primarily to bacterial fermentation of fecal carbohydrate. The rise begins immediately and is reduced, but not prevented, by refrigeration.[5] Since the rise in osmolality during storage is by generation of solute that was not present while fecal fluid was in the gut lumen, and since fecal monovalent ions do not change during storage, the rise in osmolality distorts and exaggerates the magnitude of the osmotic gap that existed in fecal fluid as it was expelled from the rectum. A second problem with measuring fecal osmolality is that the value obtained differs depending on whether one uses freezing point or vapor pressure osmometry. On average, fecal osmolality by vapor pressure is lower by about 50 mOsm/kg than fecal osmolality by freezing point depression. Discrepancies of as much as 100 mOsm/kg are sometimes observed.[34]

Fortunately for present purposes, the intestine has no diluting or concentrating mechanism, and ingested fluids and digestive secretions that enter the intestinal lumen are rapidly equilibrated toward the osmolality of plasma. Since plasma osmolality rarely deviates far from 290 mOsm/kg, the osmolality of fecal fluid as it exits the rectum is also close to 290 (Fig. 49–4). Fecal osmotic gap can therefore be calculated by subtracting the combined concentrations of monovalent electrolytes from 290.

Recently, the validity of these concepts was evaluated by inducing diarrhea in normal subjects by having them ingest phenolphthalein, which causes secretory diarrhea,[35–38] and by having them ingest a variety of solutes that cause osmotic diarrhea. Normal subjects with induced diarrhea were studied rather than patients with diarrhea, because in patients there is no practical independent way of knowing the mechanism(s) of diarrhea.

The results of this study are summarized in Table 49–6.[34] In all instances of phenolphthalein-induced diarrhea, the osmotic gap was less than 50, and in each instance of diarrhea induced by magnesium hydroxide, PEG, lactulose, or sorbitol, the osmotic gap exceeded 50. Only in

Exh. D

7.

Fordtran JS, Santa Ana CA, Cleveland MB.

A low sodium solution for gastrointestinal lavage.

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A Low-Sodium Solution for Gastrointestinal Lavage

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Golytely® is a sodium sulfate–based solution used for lavage cleansing of the colon. Although most patients and physicians prefer Golytely lavage over other methods of bowel cleansing, its highly salty taste is a drawback. This report describes the development of a modified lavage solution that has a barely perceptible salty taste. This solution was developed by removing sodium sulfate, increasing the concentration of polyethylene glycol, and making minor adjustments in the concentration of other salts. Golytely, reduced sodium sulfate Golytely (Golytely-RSS), and a balanced electrolyte solution were infused into the stomachs of normal subjects. After steady-state lavage conditions were established, the rates of fluid and electrolyte absorption were measured. Average fluid absorption rate was 791 ml/h with the balanced electrolyte solution, compared with only 63 and 45 ml/h with Golytely and Golytely-RSS, respectively. Golytely-RSS was studied at 3 infusion rates, from 0.9–1.8 L/h, and the time and volume of solution required for colon cleansing was determined; the lower infusion rate (0.9 L/h) took longer but required less solution to cleanse the colon. In conclusion, Golytely-RSS has the essential feature of Golytely; i.e., lavage is associated with negligible salt and water absorption. The less-salty taste of Golytely-RSS may make it less difficult to drink and thereby enhance patient compliance; the total volume of solution required for cleansing is less when the solution is ingested at 0.9 L/h than when the ingestion rate is 1.8 L/h.

Before 1980, gastrointestinal lavage for bowel cleansing involved ingestion of isotonic saline. A significant fraction of the ingested solution was absorbed, creating a hazard to patients who are unable to normally excrete large salt and water loads. Golytely is a gastrointestinal lavage solution that was designed to minimize salt and water absorption (1). The most important ingredient is sodium sulfate. Sulfate is a poorly absorbed divalent anion, and sodium absorption is markedly reduced when sulfate, rather than chloride and bicarbonate, is the predominant intraluminal anion. Golytely also contains sodium chloride, sodium bicarbonate, and potassium chloride; its sodium concentration is 125 mEq/L. Sixty grams of polyethylene glycol per liter, a quantity sufficient to contribute 50 mosmol/kg to osmolality, is added to achieve isotonicity with plasma. Although most patients and physicians prefer Golytely lavage to enemas and laxatives (2–9), its highly salty taste is a drawback.

The purposes of the present paper are twofold. First, we describe the development of a modified lavage solution that has the essential feature of Golytely (negligible salt and water absorption) and yet has a barely perceptible salty taste because its sodium concentration is only 65 mEq/L. This solution was developed by removing sodium sulfate, increasing the concentration of polyethylene glycol (PEG), and adjusting the concentration of the other salts. The special osmotic behavior of PEG (10) allowed this to be done with only a modest increase in the concentration of PEG. Second, using the new solution, which we call reduced sodium sulfate Golytely (Golytely-RSS), we determined the length of time and volume of solution required to cleanse the colon thoroughly at three different intragastric infusion rates, from 0.9–1.8 L/h. Such information should help evaluate the pros and cons of rapid vs. less-rapid ingestion rates of lavage solutions.

Abbreviations used in this paper: BSP, sulfobromophthalein; Golytely-RSS, reduced sodium sulfate Golytely; PEG, polyethylene glycol.

Golytely is a registered trademark of Braintree Laboratories, Inc., Braintree, Massachusetts.

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Materials and Methods

Subjects

These experiments were conducted in normal healthy volunteers who were paid a fee for their participation in this research. The study was approved by the Human Research Review Committee of Baylor University Medical Center.

Test Solutions

The compositions of the test solutions used are listed in Table 1. PEG 3350 was obtained from J.T. Baker Company (Jackson, Tenn.).

Measurement of Salt and Water Absorption

Absorption rates were measured by steady-state total gut perfusion, as previously described (1,11). Solutions were infused into the stomach at a pump speed of 15, 20, or 30 ml/min (0.9, 1.2 or 1.8 L/h). Actual measured infusion rates were determined from the volume of fluid infused over the length of the study period; these differed only slightly from the pump speed settings. As the intragastric infusions were begun, 200 mg of sulfobromophthalein (BSP) was injected into the stomach through the infusion tube. When watery diarrhea ensued, the stool specimens were checked for BSP by alkalinization with sodium hydroxide. When all BSP had been eliminated, we assumed that a steady state of perfusion had been achieved. The rectal effluent became clear of all visible fecal material about 30 min before BSP disappeared. The perfusion was continued for 3 h after BSP disappeared from the lavage effluent, during which time 6 30-min collections were obtained; the PEG concentrations in these 6 samples were essentially the same, giving further evidence of a steady state. Lavage effluent in the 6 samples were analyzed for PEG and electrolytes by previously described methods (1,11). Net absorption or secretion of water and electrolytes was calculated by standard nonabsorbable marker equations.

These studies were conducted after an overnight fast. For Golytely and Golytely-RSS studies, the subjects received no preparation other than the overnight fast. For the balanced electrolyte solution studies, the subjects ingested mannitol Golytely (PEG replaced by mannitol, as described in reference 1) during the evening before the study to cleanse the colon and thereby shorten the time required to establish steady-state conditions during the subsequent experiment. This was done because cleansing the colon with the balanced electrolyte solute, achieving a steady state, and then continuing the perfusion for an additional 3 hours (for measurement of absorption rate in the steady state) was possibly hazardous due to the large fluid and salt loads which are absorbed.

Data Analysis

Group differences were analyzed by one-way analysis of variance or t-tests with a Bonferroni correction where appropriate (12); $p < 0.05$ was considered significant.

Results

Preliminary Studies

If an isoosmotic solution of pure PEG were used as a lavage solution, plasma solutes would diffuse into the lumen down steep concentration gradients and be washed away during the lavage procedure. The effective osmotic measure of such a solution would be much higher than that of plasma (13), and there would therefore be large osmotic-induced water losses as well. To prevent such losses, electrolytes must be added to the ingested solution, and the concentration of PEG must be reduced. By trial and error, involving 5 preliminary studies, we arrived at the Golytely-RSS solution described in Table 1. The modified solution has a PEG concentration of 105 g/L, compared with 60 g/L in Golytely; its sodium concentration is 65 mEq/L and its osmolality by freezing point osmometry is 288 mosmol/kg.

Water and Electrolyte Absorption/Secretion With Various Test Solutions

Average results are depicted in Table 2. During perfusion of a balanced electrolyte solution (1.8 L/h), water absorption averaged 791 ml/h. By contrast, perfusion of Golytely (1.8 L/h) and Golytely-RSS (0.9, 1.2, or 1.8 L/hr) was associated with average rates of water absorption of 63 and 45 ml/h, respectively. Comparison of Golytely and Golytely-RSS revealed no significant differences between the two solutions with respect to water, sodium, and chloride movement. Significant ($p < 0.01$) differences do exist with regard to potassium and bicarbonate movements, but these are numerically small. With the exception of water and chloride, none of the movements associated with Golytely-RSS are significantly different from zero. Results with Golytely-RSS at the three infusion

Table 1. Composition of Solutions

Solution	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	$SO_4^=$ (mEq/L)	PEG[a] (g/L)	Osmolality[b] (mosmol/kg)
Balanced electrolyte	140	4	104	40	0	2	270
Golytely	125	10	35	20	40	60	280
Golytely-RSS	65	5	53	17	0	105	288

[a]PEG 3350. [b]Osmolality of the solutions was determined by freezing point osmometry

Table 2. Net Movement of Water and Electrolytes During Steady-State Perfusion

	Pump Speed (L/h)	n	H_2O (ml/h)	Net movement* (mEq/h) Na^+	K^+	Cl^-	HCO_3^-
Comparison of 3 solutions							
Balanced electrolyte	1.8	17	−791 ± 34	−111 ± 5.1	−2.0 ± 0.2	−71 ± 1.7	−41 ± 1.6
Golytely	1.8	14	−63 ± 26	−5.2 ± 3.6	−2.0 ± 0.8	+6.8 ± 3.5	−8.2 ± 0.8
Golytely-RSS	1.8, 1.2, and 0.9	21	−45 ± 22	+3.9 ± 2.9	0.00 ± 0.2	+8.4 ± 3.3	+0.8 ± 0.8
Probability (ANOVA), all solutions			<0.01	<0.01	<0.01	<0.01	<0.01
Probability (t-test), Golytely vs. Golytely-RSS			NS	NS	<0.01	NS	<0.01
Comparison of infusion rates							
Golytely-RSS	1.8	7	−36 ± 43	+5.2 ± 5.8	+0.7 ± 0.4	+16.2 ± 5.9	−0.2 ± 1.2
Golytely-RSS	1.2	7	−46 ± 44	+4.8 ± 5.6	−0.8 ± 0.3	+9.9 ± 5.8	+1.2 ± 0.9
Golytely-RSS	0.9	7	−54 ± 29	+1.9 ± 4.1	−0.1 ± 0.1	−0.9 ± 4.1	+1.2 ± 0.8
Probability (ANOVA), all rates			NS	NS	<0.05	NS	NS
Probability (t-test), 0.9 vs. 1.8			NS	NS	NS	NS	NS

ANOVA, analysis of variance. Table entries are given as mean ± SE. *Minus signs denote net absorption; plus signs denote net secretion.

rates were similar and not significantly different except for potassium movement, where the differences are small.

The individual values for net water and sodium movement are shown in Figure 1. The range of water and sodium absorption or secretion rates were similar with Golytely and Golytely-RSS, with no subject absorbing or secreting more than 228 ml/h. By contrast, with a balanced electrolyte solution some subjects absorbed more than 1 L/h.

Time and Volume Required for Complete Sulfobromophthalein Clearance

Sulfobromophthalein was injected into the stomach as the intragastric infusion of lavage solutions was started. The length of the infusion and the volume of fluid that had been infused when BSP disappeared from the rectal effluent are shown in Table 3. Results with the balanced electrolyte solution are not provided because studies with this solution were conducted after preliminary colon cleansing (for reasons explained in Materials and Methods). Results for Golytely and Golytely-RSS were similar when the solutions were infused at a rate of 1.8 L/h. When Golytely-RSS was infused at 1.8 L/h, BSP disappeared in about 3 hours, compared with about 4 hours when this solution was perfused at a rate of 1.2 or 0.9 L/h ($p < 0.01$). The volume of solution infused when BSP disappeared decreased as the infusion rate was decreased, from 5.34 L at 1.8 L/h to 3.76 L at 0.9 L/h ($p < 0.05$).

Other Observations

The effects of lavage with a balanced electrolyte solution and with Golytely on serum electrolytes and hematocrit have been previously reported (1). There were no clinically significant changes in serum electrolytes or hematocrit during lavage with Golytely-RSS. There was no gain or loss of weight following Golytely-RSS lavage.

Discussion

The major objective of this research was to develop a solution for gastrointestinal lavage that would have two features: (a) be associated with negligible net absorption or net secretion of water and electrolytes, and (b) have a much lower sodium concentration than Golytely to reduce the salty taste. These objectives were accomplished by omitting sodium sulfate, increasing the concentration of PEG, and making minor adjustments in the concentrations of other ions. The unusual colligative properties of PEG (10) allowed this to be done with only a modest increase in the concentration of PEG, from 60 g/L with Golytely (PEG contribution to osmolality = ~50 mosmol/kg) to 105 g/L with Golytely-RSS (PEG contribution to osmolality = ~148 mosmol/kg).

Lavage with both Golytely and Golytely-RSS was associated with near-zero average rates of water and electrolyte absorption. However, this does not mean that all subjects had zero or near-zero absorption rates. Presumably because of variations among people with regard to ion transport capacities and intestinal permeability, some subjects absorbed or secreted as much as 228 ml of fluid per h. Given that in practice (for colon cleansing) the lavage lasts for 2–3 h, this could mean that up to 684 ml of water and 30 mEq of sodium could be gained or lost to the body. Such shifts are substantially less than are known to occur with laxatives and enemas (14,15) and much less than occur with balanced electrolyte solution lavage (Figure 1), in which some subjects absorb more than 1 L of fluid per

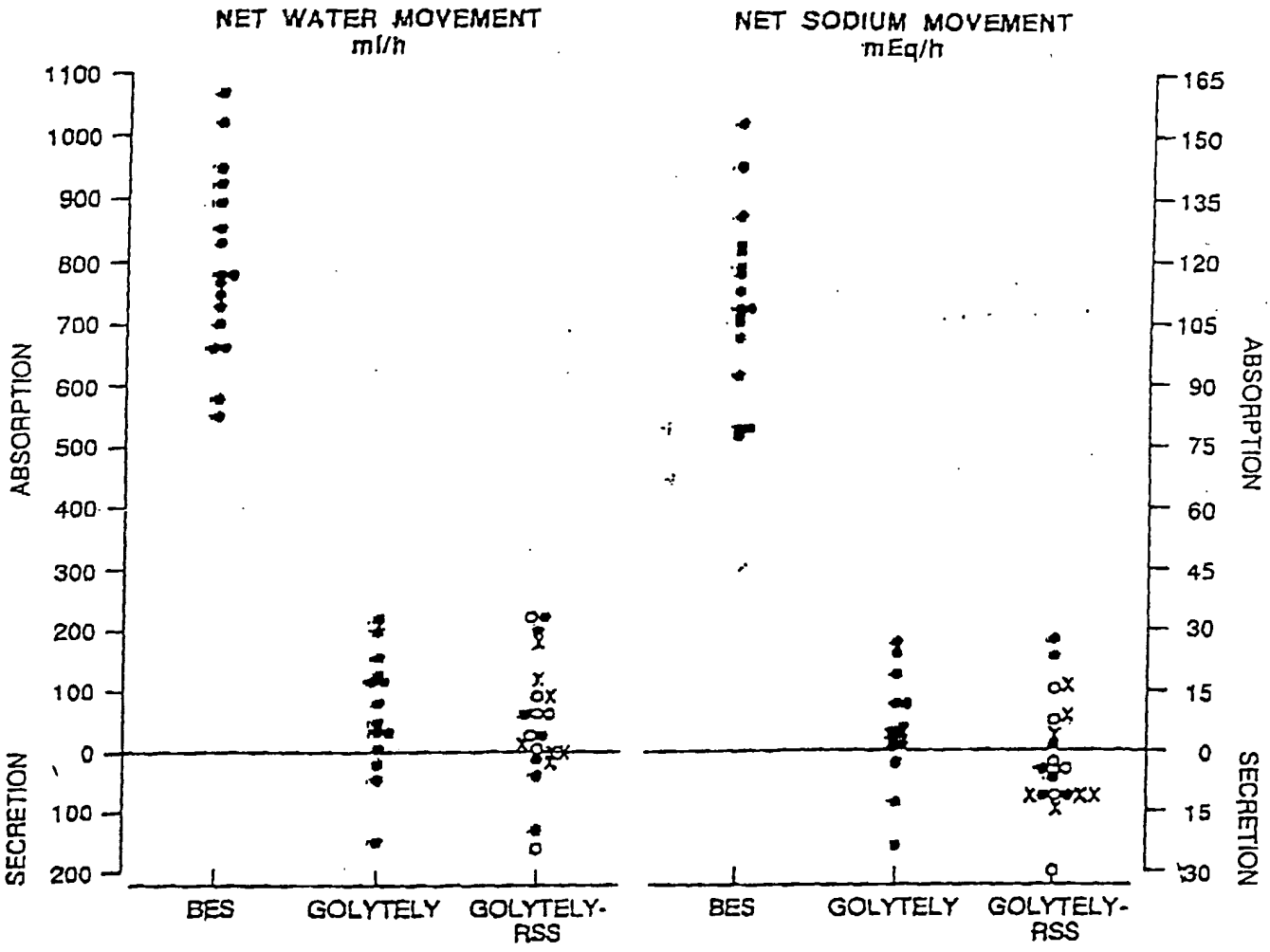

Figure 1. Net water and sodium movement during steady-state perfusion of the gastrointestinal tract; results in individual subjects. (●): Studies in which the solution was infused into the stomach at a rate of 30 ml/min (1.8 L/h); (○) infusion at 20 ml/min (1.2 L/h); X: infusion at 15 ml/min (0.9 L/h).

h (more than 3 L if such solutions were ingested over a 3-h period)

It is interesting to consider the different mechanisms by which Golytely and Golytely-RSS lavage are associated with minimal absorption or secretion. Sodium is actively absorbed by the intestine when its accompanying anion is chloride (16), but active sodium absorption is markedly reduced when sulfate is substituted for chloride (17). Moreover, sulfate is a poorly absorbed anion (18–21); as sodium is actively absorbed, sulfate cannot follow passively, leading to changes in electrical potential (luminal side negative) across the mucosa (22) that secondarily inhibit further net sodium absorption. Sulfate inhibition of sodium

Table 3. Time and Volume Required to Completely Clear the Intestine of Sulfobromophthalein

Solution	Pump Speed (L/h)	Pump Speed (ml/min)	Measured Infusion Rate (ml/min)	Time (h)	Volume (L)
Golytely, n = 14	1.8	30	28.6 ± 0.6	3.07 ± 0.2	5.23 ± 0.4
Golytely-RSS, n = 7	1.8	30	30.0 ± 0.2	2.99 ± 0.2	5.34 ± 0.4
Golytely-RSS, n = 7	1.2	20	20.5 ± 0.3	3.98 ± 0.3	4.89 ± 0.6
Golytely-RSS, n = 7	0.9	15	15.7 ± 0.1	3.98 ± 0.3	3.76 ± 0.3

Table entries are given as mean ± SE

absorption is the major mechanism by which Golytely lavage is associated with negligible fluid and electrolyte absorption. The principles governing fluid and electrolyte movement with Golytely-RSS are different. In contrast to Golytely, with Golytely-RSS lavage the luminal sodium concentration is much lower than that in plasma and there is no poorly absorbable anion. The low sodium concentration of luminal fluid creates a concentration gradient against which sodium must be absorbed, which reduces net sodium absorption (16). The rate of sodium absorption is balanced by the rate of passive sodium secretion (down the concentration gradient), resulting in near-zero net sodium movement. PEG, a very poorly absorbable nonelectrolyte (10,21), is present in the solution to increase the effective osmotic pressure and thereby prevent water absorption, which if it occurred would contract luminal volume and cause luminal sodium concentration to increase, which in turn would result in sodium absorption. Because the sodium concentration of luminal fluid is much lower than that of plasma, diffusion potentials cause the mucosal side of the intestine to be electrically positive (20). Mucosal positivity favors absorption of potassium and secretion of chloride: therefore, it was necessary to reduce the potassium concentration and increase the chloride concentration of Golytely-RSS to keep net potassium and chloride movements at zero.

In spite of these different mechanisms of action, the clinical results of lavage by Golytely and Golytely-RSS are similar, i.e., cleansing of the intestine with negligible absorption or secretion of fluid and electrolytes. Small differences in potassium and bicarbonate absorption or secretion rates were noted, both in directions favoring (i.e., nearer zero movement) Golytely-RSS. It is hoped that the less-salty taste of Golytely-RSS will improve patient compliance. Unpublished results (J. A. DiPalma, personal communication, March 1989) have shown that in blinded trials, most patients undergoing lavage for colonoscopy prefer the taste of Golytely-RSS over Golytely and that colon cleansing with the two solutions is equal.

A second purpose of these studies was to measure the length of time and volume of infused solution required to cleanse the colon at three different infusion rates. Because the gross appearance of rectal effluent is subjective, we used as our endpoint the time required to remove completely BSP that had been injected into the stomach at the start of the intragastric infusion. Sulfabromophthalein clearance from the rectal effluent is an objective measure of the time required to cleanse the intestine thoroughly. When the solution was infused at 0.9 L/h, the time required to cleanse the colon was about 1 h longer than when the infusion rate was 1.8 L/h (about 4 vs. about 3 h). However, the volume of infused solution required to cleanse the colon was about 1.5 L less when the infusion rate was 0.9 L/h than when infusion rate was 1.8 L/h (5.34 vs. 3.76 L). The times and volumes reported here do not exactly reflect the times and volumes used in clinical practice because we continued the infusion right up to the time that BSP was totally cleared from the lavage effluent. In practice, times and volumes for complete cleansing would be somewhat less because colon lavage continues for a period of time after solution ingestion has been discontinued. Nevertheless, the times and volumes we have presented should correlate qualitatively with times and volumes used in clinical practice. To the extent that a large volume of fluid ingested (rather than the time of ingestion) represents the most difficult aspect of lavage cleansing, a 0.9-L/h ingestion rate (rather than the commonly recommended 1.8-L/h ingestion rate) should improve patient acceptance.

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Exh. E

A Comparison of the Effectiveness and Patient Tolerance of Oral Sodium Phosphate, Castor Oil, and Standard Electrolyte Lavage for Colonoscopy or Sigmoidoscopy Preparation

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One hundred thirteen patients were randomized to receive either oral sodium phosphate (Fleet Phospho-Soda), lemon-flavored castor oil (Purge), or standard polyethylene glycol-based lavage solution (GoLYTELY) before elective colonoscopy. The study purpose was to confirm the efficacy of oral sodium phosphate and extend observations to include castor oil. Overall, patients reported that sodium phosphate and castor oil were easier to complete ($p < 0.05$). Scores for cleansing the entire colon as determined by endoscopists who were blinded to the cathartic agent were highest in patients receiving sodium phosphate ($p < 0.02$). Scores of left-colon cleansing for flexible sigmoidoscopy were equally high for the three methods. Scores for taste and symptom side effects were similar for each preparation. There were no recognized signs or symptoms of hypocalcemia in the sodium phosphate group. Because of the low cost of oral sodium phosphate combined with the lowest repeat endoscopy rate for inadequate cleansing, patient savings were projected to be $5000 per 100 patients at this center. Oral sodium phosphate is a cost-effective colonoscopy preparation that is better tolerated and more effective than the polyethylene glycol-electrolyte lavage solution or castor oil.

INTRODUCTION

Osmotically balanced, polyethylene glycol (PEG)-based solutions have replaced the rigorous pre-1980 colonoscopy preparations that consisted of 2 days of enemas, clear liquid diet, and laxatives in various combinations. Patients tolerate the electrolyte lavages (GoLYTELY, CoLYTE, and Klean Prep) better than the standard 2-day cleansing methods (1–4).

When compared with large-volume saline solutions, electrolyte lavage is safer due in part to reduced fluid shifts between the gut lumen and the systemic circulation (1–4). However, the large volume of electrolyte lavage can reduce patient compliance. As an example: from this center in 1989, 20% of colonoscopy preparations were inadequate to rule out diminutive polyps and arteriovenous malformations. One-third of those (7%) required another catharsis. Flavored and less salty lavage solutions have been recently introduced. However, blinded studies report no improvement in colon cleansing scores or patient tolerance (5, 6).

In 1990, a report from Vanner *et al.* (7) was the first to describe the efficacy and safety of oral sodium phosphate as a colonoscopy preparation. Although sodium phosphate was better tolerated and more effective than GoLYTELY, it is still not widely accepted for colon cleansing. There are currently no studies confirming the observations of Vanner *et al.* Furthermore, there are no studies examining the tolerance and efficacy of castor oil as a colonoscopy preparation method. This study was undertaken to compare the efficacy of small-volume preparations, oral sodium phosphate, and castor oil, with the large-volume standard PEG-electrolyte lavage.

METHODS

Demographics

One hundred thirteen (113) consecutive outpatients, requiring an elective colonoscopy and consenting to enter the study, were recruited in an 8-month period from April to December 1991. They were prospectively randomized to receive either oral electrolyte lavage (n = 38), sodium phosphate (n = 34), or castor oil (n = 41).

Exclusion criteria included acute diverticulitis, active inflammatory bowel disease, unstable cardiovascular or respiratory status, allergies to all available conscious sedation medications, myocardial infarction or cerebrovascular accident in the last 2 months, serum creatinine greater than 2.0 mg/dl, massive ascites, or delayed

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gastric emptying. Patient age, gender, and indication for elective colonoscopy are listed in Table 1.

The study was approved by the University of Florida Health Science Center at Jacksonville Institutional Review Board for human experimentation. All patients gave written informed consent.

Study solutions

Following enrollment in the study, a physician gave general instructions to each subject. Patients received a liquid diet the day before the procedure and remained *non per os* after midnight. To maintain physician blinding, the colonoscopy preparations with printed instructions were distributed by the pharmacist after randomization. Those patients randomized to the electrolyte lavage received 4 L of GoLYTELY (Braintree Pharmaceuticals; containing 236 g PEG 3350, 22.74 g sodium sulfate, 6.74 g sodium bicarbonate, 5.86 g sodium chloride, and 2.97 g potassium chloride). They were instructed to begin the preparation at 6 PM by drinking an 8-oz glass every 10 min until the 4 L were consumed. Those patients randomized to the sodium phosphate method received 45 ml of Fleet Phospho-Soda (Fleet Pharmaceuticals; containing 48 g $Na(PO_4)_2$ + 18 g $NaHPO_4$/100 ml) diluted 1:1 with water (total of 90 ml; 64 mg phosphorus/ml) at 6 PM the evening before the procedure and at 6 AM the morning of the procedure. The patients were instructed to drink at least three 12-oz glasses of water 1 h after the 6 PM dose. The castor oil group received 60 ml of Purge (Fleming and Company) containing 95% castor oil with a lemon flavoring) at 6 PM the evening before the procedure. These patients were also instructed to drink at least three 12-oz glasses of water 1 h after the 6 PM dose.

Patient acceptance

The day of endoscopy, each patient completed a questionnaire under the supervision of a nurse research coordinator. Patients ranked the ease of completing the preparation (tolerance), by choosing one of five categories: easy, tolerable, slightly difficult, extremely difficult, and unable to finish. In addition, they ranked the severity of specific symptoms as none = 0, mild (nausea and bloating) = 1, moderate (mild cramps with vomiting) = 2, and severe (significant cramps with vomiting) = 3. Taste was rated by choosing one of the following categories: excellent, good, tolerable, barely tolerable, or unacceptable.

TABLE 1
Demographics on 113 Outpatients Having Elective Colonoscopy

Category	Groups		
	Electrolyte lavage	Sodium phosphate	Castor oil
Number	38	34	41
Age (range)	58 (23–84)	52 (25–79)	51 (17–78)
Sex			
Male	20	7	17
Female	18	27	24
Indications (%)			
GI bleed	32	32	44
Polyps	45	44	29
Anemia	2	6	3
Diarrhea	5	3	17
Constipation	5	3	0
Other	11	12	7

Prep quality

Following the procedure, a Gastroenterology fellow and a faculty member jointly recorded the quality of colon cleansing. The quality grades were excellent (small volume of liquid easily aspirated, but covering less than 5% of the colonic surface), good (volume of clear liquid covering 5–25% of the surface but could be easily aspirated to expose nearly all the mucosa), fair (stool limited the examination but 90% or more of the mucosa could be examined), and poor (less than 90% of the mucosa could be examined). The Gastroenterology fellows and attending faculty remained blinded to the type of preparation and the questionnaire results.

Assessment of safety

After the questionnaire was completed and before receiving iv sedation, each patient was questioned about symptoms of fainting, light headedness, paresthesias, palpitations, muscle spasms of the extremities, or seizures that might suggest symptomatic hypocalcemia due to hyperphosphatemia. During the pre- and post-procedure periods in the endoscopy suite and the recovery area, patients were monitored electronically for hypotension, and visually for tetany, laryngospasm, muscle cramps, and convulsions.

The effect of oral sodium phosphate catharsis on serum calcium and phosphate levels was evaluated in five additional patients. Blood samples were drawn before dosing as a baseline, at 8 AM (2 h after the second dose) and 4 PM (10 h after the second dose) the day of the colonoscopy, and at 8 AM the following day (26 h after dosing).

Statistical analysis

Significance of the questionnaire responses was analyzed by the Pearson χ^2 method and the Kruskal-Wallis nonparametric analysis of variance. A p value less than 0.05 was considered significant.

RESULTS

The three patient populations were comparable in all demographic criteria except for the male:female ratio in the sodium phosphate group (see Table 1). The female preponderance in this group did not appear to bias the study in any observable manner, since the

colonoscopy indications were similar to the other groups.

Scores for patient tolerance (ease of completing the preparation) are shown in Figure 1. Thirty-nine percent described the ease of completing the electrolyte lavage as easy and 26% as tolerable compared with 44% and 44% for the sodium phosphate solution, or 56% and 27% for castor oil, respectively. The differences were not significant. However, when the data for easy and tolerable ratings were combined, both the sodium phosphate solution (88%) and the castor oil (83%) were rated significantly better than the electrolyte lavage (66%) ($p < 0.02$). The percentage of patients unable to finish the preparation was not different among the three groups (3% for the electrolyte lavage, 0% for the phosphate method, and 5% for castor oil).

In the evaluation of taste, there were no differences found between the groups as shown in Figure 2. More than 70% of the patients in the three groups rated the taste as tolerable or better (76% for GoLYTELY, 78% for castor oil, and 71% for sodium phosphate). For the evaluation of symptom side effects, there were again no differences found between the groups as shown in Figure 3.

The quality of colon cleansing for the three preparations is presented in Figure 4. Oral sodium phosphate solution was better in achieving an excellent (38%) or good (41%) cleansing score compared with the electrolyte lavage (32% and 29%) or with castor oil (20% and 12%). The differences were not significant. Since a good cleansing score, *i.e.*, volume of clear liquid covering 5–25% of the mucosal surface, should be adequate for a fastidious examination after the liquid is aspirated, it was logical to combine the good and excellent results and reevaluate significance. When this was done, the oral sodium phosphate solution was statistically better in achieving an excellent or good cleansing score with 80% compared with 64% for the electrolyte lavage ($p < 0.05$) and only 32% for the castor oil group ($p < 0.05$). For the left colon, all three preparations produced an excellent or good rating, making them adequate for flexible sigmoidoscopy examination as shown in Figure 5.

Serum calcium and phosphate levels in response to sodium phosphate preparation are shown in Figure 6. Mean serum phosphate level increased significantly 2 h after the second dose by 3.5 ± 1.64 mg/dl (mean increase, ±1 SD) but returned to normal within 26 h. There was no significant change in the mean serum calcium concentration. None of the patients taking the oral sodium phosphate solution reported or demonstrated signs or symptoms of hypocalcemia.

At this center, the charges for the colonoscopy cleansing solutions were: electrolyte lavage, $17; sodium

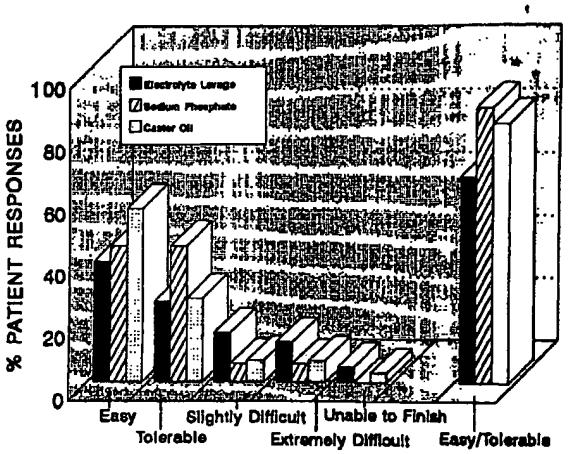

FIG. 1. Patient evaluation of the ease of completing the electrolyte lavage, oral sodium phosphate, or castor oil, *i.e.*, tolerance. Questionnaire options are listed in the *horizontal axis*, with the number of patients responding to each expressed as a percentage. When easy and tolerable results were combined, sodium phosphate and castor oil were significantly easier than the lavage to complete (*, $p < 0.02$).

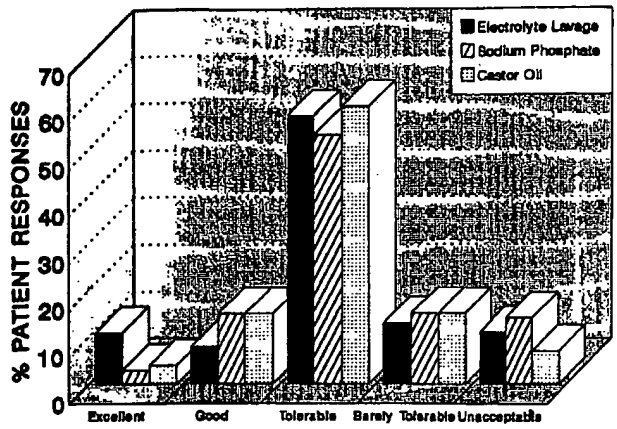

FIG. 2. Patient evaluation of preparation taste. Questionnaire options are listed in the *horizontal axis* with the percentage of patients indicating the response in *bar* format. Analysis of individual responses or combinations did not disclose any significant differences.

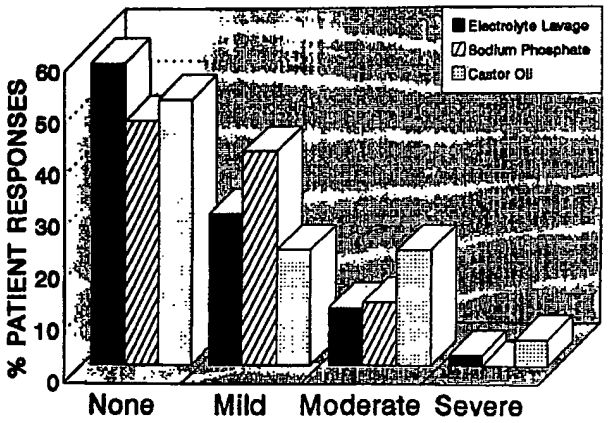

FIG. 3. Patients' rating of the symptom side effects from each preparation. Questionnaire options are listed on the *horizontal axis*, and the number of patients reporting side effects are reported as percentages. Analysis of individual responses or combinations did not disclose any significant differences.

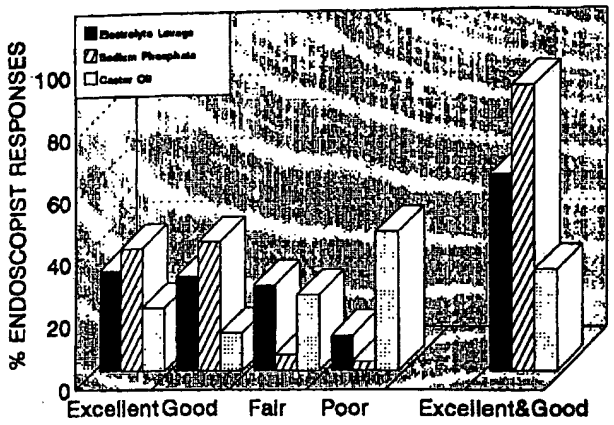

FIG. 4. Number rating of the adequacy of colonic cleansing (Prep Quality). Questionnaire options are listed on the *horizontal axis*, with the number of patients rated in each category shown as a percentage. When good and excellent scores were combined, sodium phosphate was significantly better than the electrolyte lavage or castor oil ($p < 0.05$).

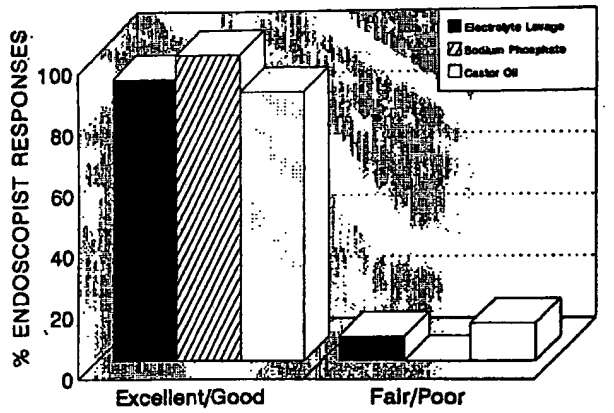

FIG. 5. Number rating of the adequacy of colonic cleansing for flexible sigmoidoscopy. The adequacy of colonic preparation is shown on the *horizontal axis* with the number of patients shown as a percentage. There were no differences between the three preparation methods.

phosphate, $2; and castor oil, $2. The endoscopy suite charge for an incomplete examination (excluding physician fees) was $900. The number of repeat procedures due to inadequate colon cleansing is shown in Figure 7. Based on a repeat examination rate for inadequate preparation of 8% for the electrolyte lavage, 3% for the sodium phosphate, and 24% for the castor oil, the excess costs (incomplete examination plus additional cathartic) projected for 100 cases are: electrolyte lavage, $7336; sodium phosphate, $2706; and castor oil, $21,648.

DISCUSSION

This study confirms and extends the observations of Vanner *et al.* (7). In that study, over 85% of patients described their ability to complete the sodium phosphate as easy or tolerable, compared with only 31% of

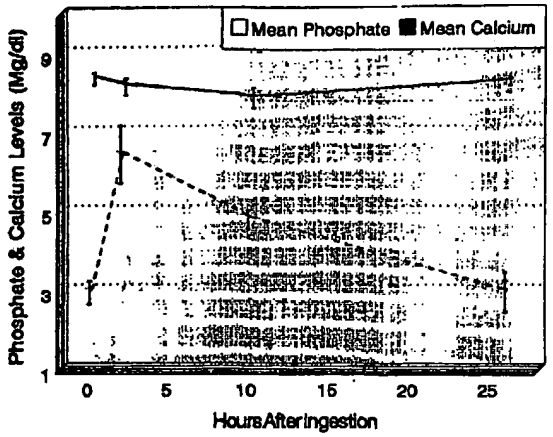

FIG. 6. Mean serum phosphate and calcium concentrations in five subjects. Time in hours after sodium phosphate ingestion is shown on the *horizontal axis*. Mean concentrations over time are marked by the *line*. The peak phosphate level was recorded at 8 AM, 2 h after the second sodium phosphate dose. At 10 h, the mean phosphate level was no longer significantly elevated compared to the mean baseline level.

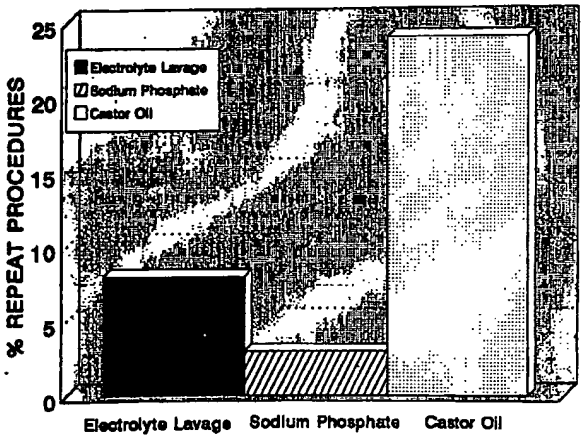

FIG. 7. The number of repeat colonoscopies due to poor colon cleansing. The type of colonic cleansing preparation is shown on the *horizontal axis* with the number of patients shown as a percentage. Castor oil was associated with more repeat examinations ($p = 0.011$).

those receiving electrolyte lavage. In our study, the difference was not as dramatic, but was still significant at 88% for sodium phosphate and 66% for the lavage ($p < 0.05$). Even castor oil, which was evaluated in this study and not by Vanner *et al.*, was also significantly better than the electrolyte lavage (83%, $p < 0.05$).

When judging taste, most patients in Vanner's study in both groups rated the taste as acceptable (sodium phosphate, 68%; electrolyte lavage, 66%). However, 31% of those receiving the electrolyte lavage rated it as unacceptable or barely acceptable compared with 13% of those receiving sodium phosphate. Nineteen percent of those receiving sodium phosphate ranked it as excellent or good tasting compared with 3% of those receiving the lavage ($p < 0.05$). Most of the patients in our study also rated each preparation as acceptable (sodium

phosphate, 71%; electrolyte lavage, 76%; and castor oil, 78%). There were no differences in the scores of excellent and good (sodium phosphate, 18%; lavage, 18%; castor oil, 20%) or of unacceptable and barely acceptable (sodium phosphate, 29%; lavage, 24%; and castor oil, 22%).

Symptom side effects of nausea, vomiting, abdominal bloating, pain, and dizziness occurring during the evacuation of the colon did not differ in the sodium phosphate and electrolyte lavage groups in Vanner's study, nor were there differences in our study between sodium phosphate, electrolyte lavage, and castor oil.

Although ease of taking the preparations marginally favored sodium phosphate and castor oil over the lavage, with taste or symptom side effects being equivalent, the most important finding was the superiority of sodium phosphate over the electrolyte lavage in cleansing the colon. In the previous study (7), over 80% of the sodium phosphate-prepared colons were ranked as good or excellent, compared with only 33% of the electrolyte lavage preparations. Twenty percent of the patients taking the lavage were unable to complete their preparation. In our study, colon cleansing scores of good or excellent were seen in 90% receiving sodium phosphate, 62% receiving the electrolyte lavage, and 33% receiving castor oil. All patients were able to complete the sodium phosphate preparation in our study but 5% of patients taking the lavage and 2% taking castor oil failed to complete the preparation (Fig. 1). These differences were not significant.

Despite the apparent advantages of oral sodium phosphate over the electrolyte lavage identified in the study by Vanner *et al.* (7) and in the current study, this preparation has not gained wide acceptance. Although there are no reports of deaths or significant toxicity from oral sodium phosphate used in the preparation of colonoscopies, it is possible that the lessons learned from complications of enema use have limited a broader application to colonoscopy preparation. In the pediatric literature, many examples of dehydration, tetany, and coma have been reported in infants and small children (8–18). Risk factors included colonic retention due to Hirschsprung's disease, delayed excretion from renal failure, and excessive enema doses. Tetany, mental confusion, and dehydration have been described in at least eight adults (19–25). Colonic dysfunction, renal failure, or multiple enemas explained many of the complications. In one patient, enhanced absorption due to ischemic colitis was suspected (20). In another, a myocardial infarction resulting from osmotic catharsis-induced hypovolemia was suspected (25).

There are no reports of these potentially serious side effects from oral sodium phosphate. Being a minimally absorbed osmotic cathartic agent, sodium phosphate produces a large volume effluent with the potential risk for reducing intravascular volume (26). Vanner *et al.* (7) showed that six of 54 patients (11%) receiving sodium phosphate and one of 48 (2%) patients using the electrolyte lavage developed a postural increase in pulse greater than 10 beats/min. Four of 54 (7%) and two of 48 patients (4%) developed a postural drop in systolic blood pressure greater than 10 mm Hg. These hemodynamic changes usually lasted less than 1 h and caused no clinical sequelae. Factors such as age, medications, or underlying diseases did not identify patients at risk for these changes in pulse and blood pressure (7). Conclusions to be drawn include cautious use orally in patients with symptomatic congestive heart failure, ascites, or a serum creatinine >2.0 mg/dl, since even minimal changes in intravascular volume may have exaggerated effects. Additional fluid intake such as three 12-oz glasses of water after their first dose (6 PM) may minimize intravascular volume changes.

Hyperphosphatemia is a recognized consequence of sodium phosphate use (27). This study and the previous study (7) detected a transient rise in the phosphate level without apparent effect on serum calcium levels. The mean incremental increase in serum phosphate level of 3.5 mg/dl in the five patients studied was identical to the increase reported in Vanner's study. Eight to 10 h later, the phosphate levels had returned to normal. There were no significant changes in serum calcium concentrations.

Three additional restrictions to the use of sodium phosphate should be emphasized. Sodium phosphate should not be used in pregnant or breast-feeding women. The placenta actively transports phosphate and it is secreted in large amount in milk (27). There is no information about absorption in diseased bowel, although toxicity in ischemic colitis has been implicated (20). When patients with these risk factors are identified and excluded, sodium phosphate appears to be safe and effective.

Castor oil, derived from the castor bean, is hydrolyzed by pancreatic lipase to the active agent, ricinoleic acid. Ricinoleic acid, acting like other anionic surfactants, reduces net absorption of fluid and electrolytes and stimulates intestinal peristalsis (27). Because it acts in the small intestine, accumulation of fluid and evacuation are prompt and thorough making it useful as a preparation for radiologic examinations. During a review of articles published in the last decade, we found no studies prospectively analyzing the efficacy of castor oil for colonoscopies. Thus, the current study appears to be the first prospective review of castor oil as a colonoscopy preparation. Unfortunately, at the dose used in this study, it was no better than sodium phosphate in patient tolerance, taste, or symptomatic side effects and was the least effective in bowel cleansing

(Fig. 6). A possible role for castor oil may exist as a small-volume preparation for flexible sigmoidoscopies, but even in this situation, it is no better than sodium phosphate (Fig. 5). The stimulant effects of this agent can cause uterine contraction in pregnant women; therefore, pregnancy is a contraindication for its use (26).

Cost to the patient is an important issue today. At this center, the excess cost due to incomplete examinations was the least for the sodium phosphate preparation ($2706 per 100 cases). This could result in a net patient savings of greater than $5000, using sodium phosphate instead of the electrolyte lavage or castor oil, or more than $30,000 annually at this institution.

In summary, this physician-blinded prospective study of three colonoscopy preparations demonstrated that sodium phosphate was better tolerated and more effective in colonic cleansing than electrolyte lavage or castor oil. There were no apparent adverse effects due to hyperphosphatemia or hypocalcemia in patients taking the sodium phosphate preparation as prescribed in this study. Furthermore, the superior cleansing quality of this preparation could save patients over $5000 per 100 colonoscopies, compared with the other two preparations. In the setting of outpatient endoscopy performed on patients with no risk of adverse events, as described in our exclusion criteria, sodium phosphate may be the preparation of choice.

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